the specification which comply with 37 C.F.R. §1.821-1.825 and, therefore, assert that the objection has been obviated.

II. REJECTIONS UNDER 35 U.S.C. §112, ¶2

The examiner rejects claims 63-65 under 35 U.S.C. §112, ¶2, for allegedly being indefinite. Applicants respectfully traverse the rejection.

According to the examiner, "[n]o positive active steps of the "designing" are set forth such that one of skill in the art would be able to practice the invention," and the specification provides "no definitions or examples of such designing steps." Office Action, page 3, third paragraph. The Examiner also asserts that the phrase "that forms a bond with the catalytic domain" renders the designing step unclear. Finally, the examiner asserts that it is unclear whether the determining step is performed *in vitro* or *in silico*.

The instant invention is directed to a method of identifying a compound that associates with a TACE, comprising using atomic coordinates obtained from crystallographical analysis of a catalytic domain of a TACE polypeptide to design an associating compound that forms a bond with the catalytic domain. Step (A) of the claimed method specifically requires "***using*** atomic coordinates . . . ***to design*** an associating compound." (emphasis added). Applicants assert that step (A), on its face, evokes an active designing step. Also, contrary to the Examiner's assertion, the specification provides detailed instructions for carrying out the designing step and, in particular, identifies exemplary software and binding sites. *See* Application page 20, line 24 to page 21, line 17 and page 30, line 26 to page 31, line 7. Moreover, the specification teaches that an associating compound "may bind to or interact with TACE ionically, covalently, by hydrogen bond, van der Waals interaction, salt bridges, steric interaction, hydophilic interactions and hydrophobic interaction." *Id.* at page 19, lines 8-11. Accordingly, Applicants assert that one of ordinary skill in the art would recognize that the instant methods recite a designing step and, in light of the specification, would understand the metes and bounds of the claim terms. Applicants, therefore, request that the rejection be withdrawn.

With regard to the 'determining' step, the specification, as discussed below, teaches that the binding characteristics of putative associating compounds can be evaluated using *in silico* or *in vitro* methodologies. Thus, Applicants aver that an artisan would recognize, in light of the specification, that former claims 63-65 encompassed methods comprising both evaluative methods and, consequently, would understand the scope of the claimed invention. To further clarify the invention, however, Applicants have amended the claims to recite either *in silico* or *in vitro* methods. Accordingly, Applicants request that the rejection be withdrawn.

The Examiner also rejects claims 41-65 under 35 U.S.C. §112, ¶2, for allegedly being incomplete for omitting essential steps. Applicants respectfully traverse the rejection.

The Examiner asserts that the inventive methods require a synthesis step prior to the determination step. Applicants respectfully disagree. The specification provides that associating compounds can be evaluated ***computationally*** prior to synthesis. *See e.g.* Application page 20, line 19; and page 22, lines 24-28. Moreover, the specification cites a variety of docking programs ideal for pre-synthesis evaluation of candidate compounds. *See* Application page 20, line 24 to page 22, line 26. Accordingly, Applicants assert that the inventive methods do not require a synthesis step prior to the evaluation of a putative compound and request that the rejection be withdrawn.

The Examiner rejects claim 43 for allegedly lacking an antecedent basis. Applicants assert that the proposed amendments obviate the rejection.

The Examiner rejects claims 44-46, 48 and 51 for allegedly being indefinite. The Examiner asserts that the antecedent basis of the phrase "said TNF-α-converting enzyme polypeptide" is unclear. Applicants respectfully disagree. The antecedent, *i.e.* "**a** TACE polypeptide," appears in step (A) of the independent claim and is distinguishable from the term "TACE" that resides in the claim's preamble. Therefore, Applicants assert that an artisan would readily recognize that the instant phrase limits the source of the atomic coordinates and, consequently, would understand the metes and bounds of the invention. Accordingly, Applicants request that the rejection be withdrawn.

The Examiner rejects claims 52, 53 and 55 for allegedly lacking antecedent basis. Applicants assert that the proposed amendments obviate the rejection.

III. REJECTIONS UNDER 35 U.S.C. §112, ¶1

The examiner rejects claims 41-65 under 35 U.S.C. §112, ¶1, alleging that the claims are not enabled by the specification. Applicants respectfully traverse the rejection.

According to the Examiner, the disclosure "does not reasonably provide enablement for designing other associating compounds to native and full length TACE." Office Action, page 4, fifth paragraph. In essence, the Examiner asserts that the crystal of the claimed invention is not indicative of a crystal of a native and full-length TACE and concludes that an artisan using the instant methods could not design, without undue experimentation, a compound that associates with a native and full-length TACE.

Under §112, the application must explain how to "make and use" the claimed invention. The courts have interpreted this statute to mean that the specification must teach the skilled artisan how to practice the invention without undue experimentation. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, the test is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of experimentation is typical in the area. *See* MPEP §2164.01 (February 2000) at page 2100-130.

Applicants assert that one of ordinary skill in the art could readily make and use the inventive methods to design, without undue experimentation, a compound that associates with a native and full-length TACE. To support this assertion and to counter the Exmaniner's conclusion, Applicants' agent provided the Examiner, at the aforementioned interview, a facsimile of a declaration by Dauphine Barone. In her declaration, which is enclosed herewith, Ms. Barone avers how she evaluated 13 compounds identified by the inventive methods as binding with the catalytic domain of a TACE polypeptide. Ms. Barone utilized an *in vivo* mouse model to assess the functionality of the compounds, *i.e.* their ability to associate with native, full-length TACE.

The data provided in the declaration indicate that 11 of the 13 compounds effectively associated with the TACE catalytic domain of a native, full-length TACE. Thus, as stressed at the interview, one of ordinary skill in the art, informed by the instant specification, could readily use applicants' inventive methodology to design, without undue experimentation, a ligand that associates with a native, full-length TACE. Accordingly, Applicants have satisfied the enablement requirement under Section 112.

IV. REJECTIONS UNDER 35 U.S.C. §102

The examiner rejects claims 41, 44, 56 and 63 under 35 U.S.C. §102(b), for allegedly being anticipated by Gomis-Ruth *et al.* (1998). Applicants respectfully traverse these rejections.

The examiner asserts that Gomis-Ruth teaches "atomic coordinates of a TACE polypeptide which ***are derived*** from a crystallographical analysis of adamlysin which was used to produce a ***theoretical*** crystal structure for the TACE polypeptide." (emphasis added) Office Action, page 6, last paragraph. The Examiner then states that the rejected claims do not require an actual crystal structure for TACE. *Id.* Applicants respectfully disagree and acknowledge the Examiner's willingness, expressed in the interview, to withdraw the rejection.

As argued in the previous response and recent interview, the claims of the present invention do not encompass crystallographical analysis of a theoretical crystal structure. To the contrary, the claims on their face require the use of atomic coordinates obtained from actual crystallographical analysis of a catalytic domain of a TACE polypeptide. As Gomis-Ruth fails to teach the use of actual atomic coordinates in designing TACE-associating compounds, the reference cannot anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejections be withdrawn.

V. STATEMENT REGARDING COMMON OWNERSHIP

Applicants concurrently file herewith an Information Disclosure Statement which cites U.S. patent No. 5,830,742. The instant application and U.S. patent No. 5,830,742 were, at the time the invention of the instant application was made, owned by Carlsberg Laboratory. Copies of the recorded assignments for both inventions are enclosed.

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In view of the foregoing remarks it is believed that the application is in condition for allowance. A favorable disposition of the application therefore is solicited. The examiner also is invited to contact the undersigned if there are any questions or if the examiner believes that further discussion will advance prosecution.

Respectfully submitted,

22 October 2001
Date

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MARKED-UP VERSIONS OF PROPOSED CLAIM AMENDMENTS

43. (Twice Amended) The method according to claim 63, wherein the **atomic** coordinates comprise the coordinates of Table 1, or a substantial part thereof.

51. (Twice Amended) The method according to claim 63, wherein **said [TNF-α-converting enzyme polypeptide has a crystal structure diffracting] crystallographical analysis employs a TACE polypeptide crystal that diffracts** to 2.0 Å.

52. (Twice Amended) The method according to claim 63, wherein **[the crystal of said TNF-α-converting enzyme polypeptide is monoclinic] said crystallographical analysis employs a TACE polypeptide crystal that is monoclinic**.

53. (Twice Amended) The method according to claim 63, wherein **[the crystal of said TNF-α-converting enzyme polypeptide has] said crystallographical analysis employs a TACE polypeptide crystal having** a unit cell comprising four crystallographically independent **[TNF-α-converting enzyme] TACE** catalytic domain (TCD) molecules.

55. (Twice Amended) The method according to claim 63, wherein **[the crystal of said TNF-α-converting enzyme polypeptide is] said crystallographical analysis employs a TACE polypeptide crystal** belonging to the monoclinic space group $P2_1$ and **[the] having** cell **[has the]** constants a=61.38 Å, b=126.27 Å, c=81.27 Å, and β=107.41°.

63. (Amended) A method of identifying a compound that associates with tumor necrosis factor-α-converting enzyme (TACE), comprising:

(A) using atomic coordinates obtained from crystallographical analysis **of a catalytic domain** of a TACE polypeptide to design an associating compound that forms a bond with **[the catalytic domain of said TACE polypeptide] said catalytic domain**; and

(B) determining **via computer-generated models** whether said compound associates with said **[TACE polypeptide] catalytic domain**.

64. (Amended) A method of identifying a compound that associates with tumor necrosis factor-α-converting enzyme (TACE), comprising:

(A) using atomic coordinates obtained from crystallographical analysis of **a catalytic domain** of a TACE polypeptide to design an associating compound that forms a bond with **[the catalytic domain of said TACE polypeptide] said catalytic domain**; and

(B) determining **via computer-generated models** whether said compound associates with said **[TACE polypeptide] catalytic domain**,

wherein said atomic coordinates comprise the coordinates of Table 1, or a substantial part thereof, and **[said TNF-α-converting enzyme polypeptide comprises the TNF-α-converting enzyme catalytic domain,**

further wherein] said associating compound is a TACE inhibitor.

65. (Amended) A method of identifying a compound that associates with tumor necrosis factor-α-converting enzyme (TACE), comprising:

(A) using atomic coordinates obtained from crystallographical analysis of **a catalytic domain** of a TACE polypeptide to design an associating compound that forms a bond with **[the catalytic domain of said TACE polypeptide] said catalytic domain**; and

(B) determining **via computer-generated models** whether said compound associates with said **[TACE polypeptide] catalytic domain**,

wherein said atomic coordinates comprise the coordinates of Table 1, or a substantial part thereof, and **[said TNF-α-converting enzyme polypeptide comprises the TNF-α-converting enzyme catalytic domain,**

further wherein] said associating compound is designed to introduce a non-polar group which occupies the S1' pocket of TNF-α-converting enzyme.

Proposed claim Amendments for USSN 09/244,984

63. (Amended) A method of identifying a compound that associates with tumor necrosis factor-α-converting enzyme (TACE), comprising:

(A) using atomic coordinates obtained from crystallographical analysis of **a catalytic domain** of a TACE polypeptide to design an associating compound that forms a bond with **[the catalytic domain of said TACE polypeptide] said catalytic domain**; and

(B) determining **via computer-generated models** whether said compound associates with said **[TACE polypeptide] catalytic domain**.

41. The method according to claim 63, wherein said associating compound is an inhibitor, mediator, or other compound that regulates TNF-α-converting enzyme activity.

42. The method of claim 41, wherein said associating compound is a competitive inhibitor, un-competitive inhibitor, or non-competitive inhibitor.

43. (Amended) The method according to claim 63, wherein the **atomic** coordinates comprise the coordinates of Table 1, or a substantial part thereof.

44. The method according to claim 63, wherein said TNF-α-converting enzyme polypeptide comprises the TNF-α-converting enzyme catalytic domain.

45. The method according to claim 63, wherein said TNF-α-converting enzyme polypeptide is the expression product of a polynucleotide encoding the pro and catalytic domains of TNF-α-converting enzyme.

46. The method according to claim 63, wherein said TNF-α-converting enzyme polypeptide is the expression product of a polynucleotide encoding the amino acid residues 1-477 of TNF-α-converting enzyme.

47. The method of claim 46, wherein the polynucleotide is substituted such that amino acid residue Ser266 is changed to Ala and amino acid residue Asn542 is changed to Gln, and wherein a second polynucleotide encoding the sequence Gly-Ser-$(His)_6$ is fused to the C-terminus.

48. The method according to claim 63, wherein said TNF-α-converting enzyme polypeptide is co-crystallized with a binding partner.

49. The method of claim 48, wherein the binding partner is a hydroxamate-based binding partner.

50. The method of claim 48, wherein the binding partner is N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2-(amino)ethyl amide.

51. (Amended) The method according to claim 63, wherein **said [TNF-α-converting enzyme polypeptide has a crystal structure diffracting]** **crystallographical analysis employs a TACE polypeptide crystal that diffracts** to 2.0 Å.

52. (Amended) The method according to claim 63, wherein **[the crystal of said TNF-α-converting enzyme polypeptide is monoclinic]** **said crystallographical analysis employs a TACE polypeptide crystal that is monoclinic**.

53. (Amended) The method according to claim 63, wherein **[the crystal of said TNF-α-converting enzyme polypeptide has]** **said crystallographical analysis employs a TACE polypeptide crystal having** a unit cell comprising four crystallographically independent **[TNF-α-converting enzyme]** **TACE** catalytic domain (TCD) molecules.

54. The method of claim 53, wherein the TCD molecules are in an asymmetric unit.

55. (Amended) The method according to claim 63, wherein **[the crystal of said TNF-α-converting enzyme polypeptide is]** **said crystallographical analysis employs a TACE polypeptide crystal** belonging to the monoclinic space group $P2_1$ and **[the]** **having** cell **[has the]** constants a=61.38 Å, b=126.27 Å, c=81.27 Å, and β=107.41°.

56. The method according to claim 63, wherein the associating compound is designed to associate with the S1' region of TNF-α-converting enzyme.

57. The method according to claim 63, wherein the associating compound is designed to associate with the S1'S3' pocket of TNF-α-converting enzyme.

58. The method according to claim 63, wherein the associating compound is designed to incorporate a moiety that chelates zinc.

59. The method according to claim 63, wherein the associating compound is designed to form a hydrogen bond with Leu348 or Gly349 of TNF-α-converting enzyme.

60. The method according to claim 63, wherein the associating compound is designed to introduce a non-polar group which occupies the S1' pocket of TNF-α-converting enzyme.

61. The method according to claim 63, wherein the associating compound is designed to introduce a group which lies within the channel joining S1' - S3' pockets of TNF-α-converting enzyme and which makes appropriate van der Waal contact with the channel.

62. The method according to claim 63, wherein the associating compound is designed to form a hydrogen bond with Leu348 or Gly349 on the backbone amide groups of TNF-α-converting enzyme.

Cancel claim 44 and add the following claim:

66. (NEW) A method of identifying a compound that associates with tumor necrosis factor-α-converting enzyme (TACE), comprising:

(A) using atomic coordinates obtained from crystallographical analysis of a catalytic domain of a TACE polypeptide to design an associating compound that forms a bond with said catalytic domain;

(B) synthesizing said compound; and

(C) determining in vitro whether said compound associates with said catalytic domain.

INFORMATION ON RELATED APPLICATIONS

This application claims the priority benefit of U.S. provisional patent application No. 60/073,709, filed February 4, 1998, U.S. provisional patent application No. 60/135,499, filed March 30, 1998, and U.S. provisional patent application No. 60/117,476, filed January 27, 1999.